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GRANT NUMBER DAMD17-96-1-6321

TITLE: Risk Factors for Breast Cancer and its Prognosis

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REPORT DATE: October 1997

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1997	Annual (23 Sep 96 - 22 Sep 97)

4. TITLE AND SUBTITLE
Risk Factors for Breast Cancer and its Prognosis

5. FUNDING NUMBERS
DAMD17-96-1-6321

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Statens Serum Institut
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

This project takes advantage of the high quality and population-based nature of the registries in Denmark to study reproductive risk factors for the deveopment and prognosis of breast cancer. In the first fiscal year, four studies were completed. Based on an old and population-based Danish registry of induced abortions, we defined a large cohort of 28.5 million person-years to address the issue whether induced abortion increases the risk of breast cancer. We found no overall effect of induced abortion on breast cancer risk. In study 2-4, we took advantage of a very complete Danish registry which contains population-based information on tumour characteristics, treatment regimens and follow-up status on Danish women with breast cancer. We found low age at first childbirth but not parity to be associated with a poor prognosis. Furthermore, a diagnosis of breast cancer less than two years after having given birth was associated with a particularly poor survival irrespective of the stage of disease at debut. This made us conclude that a recent pregnancy should be regarded as a negative prognostic factor and as such be considered in the counselling of these patients. Finally, we found no evidence that a pregnancy subsequent to breast cancer treatment should aggrevate the prognosis.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Breast Cancer, reproductive factors, prognosis, abortion, parity, registry linkage, Denmark	37
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

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M. Mey — Jan 12, 1988

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Papers published or in press

Melbye M, Wohlfahrt J, Olsen JH, Frisch M, Westergaard T, Helweg-Larsen K, Andersen PK. Induced abortion and the risk of breast cancer. NEJM 1997;336:81-85.

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INTRODUCTION

The general aim of this project is by use of the high quality and population-based nature of registries in Denmark to study reproductive risk factors for breast cancer and its prognosis. This first years report comprises results from the first four studies that have been completed. Several other studies are far in the proces but will be reported on in next years report. The completed studies belong to sections I (abortion and breast cancer risk) and III (factors influencing the prognosis of breast cancer) in the original application. The background and objectives of each of the four studies will be presented in this chapter followed by a comprehensive description of materials, methods, results and discussion in the following chapter (body). Conclusions will be presented in the end (conclusions).

Study 1. (belonging to section I): Induced abortion and breast cancer risk

Reproductive factors are important in breast cancer development, but their exact influence has not been established. A full-term pregnancy has been shown to increase the short-term risk of breast cancer, possibly through growth-enhancing properties of pregnancy-induced estrogens. By contrast it decreases the long-term risk, perhaps by inducing terminal differentiation of the susceptible mammary tissue.[1-5] Based primarily on animal studies, the potential for terminal differentiation of breast cells appears to be significantly lower for a pregnancy terminated by abortion compared to a full-term pregnancy. This observation led Russo et al.[3] to suggest that complete differentiation of the breast cells conveyed by a full-term pregnancy has to be achieved to provide protection against carcinogenic effects. An interrupted pregnancy, on the contrary, might increase the risk of breast cancer because proliferation of breast cells will take place without the protective effect of subsequent differentiation.

Epidemiologic studies on the association between abortion and subsequent breast cancer risk have shown inconsistent results, with risk estimates ranging from moderately elevated to significantly lowered values.[6-23] In their recently published case-control study, Daling et al. found an indication of an elevated risk in women with induced abortion between 9 to 12 weeks' gestation but this finding was based on very limited numbers.[7] In study 1, we took advantage of the mandatory registration in Denmark of gestational age-specific induced abortion history and complete reproductive history to evaluate the hypothesis by Russo.[3]

Study 2. (belonging to section 3): Time since childbirth and the prognosis of breast cancer *and* study 3. (belonging to section 3): Parity, age at first birth and the prognosis of breast cancer

An early first delivery and a large number of childbirths are among the best established factors conferring a low risk of breast cancer [1]. Recent studies have described a dual effect of full-term pregnancy on the risk of breast cancer with a transiently increased risk immediately after childbirth followed by a long-term reduction in the risk [2-4]. Although these findings relate to the risk of breast cancer development, they could very well also have implications for the prognosis of this disease. An established breast cancer prior to or during pregnancy might accelera-

te its growth under the influence of high concentrations of pregnancy hormones, primarily estrogens. However, the available literature on this point is conflicting [5-7], probably as a result of problems with small study sizes or the lack of adjustment for relevant tumour characteristics and reproductive history.

In study 2 we took advantage of three nationwide Danish registries, one containing detailed information on tumour characteristics, treatment regimes, and clinical outcome and two others containing complete parity information, to address the question of a possible influence of reproductive history on breast cancer survival.

The same registries were used in stduy 3 to further evaluate the effect of parity and age at first childbirth on the prognosis of breast cancer.

Study 4 (belonging to section III): Should women be advised against pregnancy after breast-cancer treatment?

Much attention has been given to the importance of endocrine factors on breast cancer development and prognosis since Beatson one hundred years ago first reported on the positive effect of oophorectomy in women with breast cancer [1]. A woman's reproductive history strongly influences her risk of later developing breast cancer and one of the most well-known associations is the protective effect of having a large number of children, preferable at a young age [2,3]. Whereas childbearing may overall reduce the risk of breast cancer, there is accumulating evidence that childbirth at least in some situations may have a negative effect on the prognosis of breast cancer. Thus, more studies suggest that breast cancer diagnosed during or in the first years after childbearing is associated with a poor prognostic outcome [4-6].

An outstanding question has been whether a pregnancy subsequent to breast cancer treatment may worsen the prognosis. The present literature on this subject seems to indicate that contrary to expectations, there is no negative effect of pregnancy after treatment of breast cancer. However, the evidence is weak and based on small studies which for the most part have lacked the ability to adequately adjust for important confounders [7-16]. Another important obstacle in the study of this question has been that the group of women who decide to have a child subsequent to breast cancer diagnosis is considered to be highly selected [4]. In the Western world, the median age at first childbirth has increased over the last decades. Since motherhood is generally postponed, more patients are seeking medical advice concerning pregnancy after treatment of breast cancer. In the present study we addressed the question of the prognostic influence of pregnancy subsequent to breast cancer treatment based on a linkage analysis between the population-based Danish Breast Cancer Cooperative Group (DBCG) registry and other national registries. Detailed information on stage of disease allowed us to address specifically the potential problem of selection bias.

BODY

Study 1. Induced abortion and the risk of breast cancer

Material and methods

For the purpose of the present study we performed a linkage of data from the Civil Registration System (CRS) with the National Registry for Induced Abortions, and the Danish Cancer Registry. Before initiating the study we obtained permission from the National Scientific Ethics Committee and the Data Protection Board. Since April 1, 1968, the CRS has assigned a unique identification number to all citizens in Denmark which permits accurate linkage of information from different registries. The CRS also keeps updated files on dates of livebirths and documents demographic variables such as emigration and death. Since 1939, reporting of induced abortions has been mandatory to the National Board of Health. In 1973, legal rights to induced abortion up to and including 12 weeks of gestation were established for women with residence in Denmark. Permission to have induced abortion after week 12 stated indicators such as medical, ethical (e.g. rape), eugenic, social and special personal conditions that would greatly interfere with proper handling of the newborn child. Since 1973, information on all induced abortions has been computerized in the National Registry of Induced Abortions making the information easily accessible. This registry contains information on exact date and gestational age at time of the induced abortion.[24] The methodology used for the induced abortions included in this analysis (period 1973 to 92) represented almost exclusively surgical removal. The Danish Cancer Registry contains cancer diagnoses from the entire country back to 1943. Independent reporting is taking place from clinicians, pathologists, clinics, radiotherapy units, and hospitals.[25]

A research database was established from the CRS comprising all Danish women born between April 1, 1935, and March 31, 1978, with information on live-born children. Based on the person-identifiable CRS-number a linkage was performed with the National Registry of Induced Abortions supplying information to the database on date of any induced abortion, and the gestational age of the aborted fetus. Subjects were subsequently linked with the Danish Cancer Registry to identify those diagnosed with invasive breast cancer. All women entered the follow-up for breast cancer on April 1, 1968, or on their 12th birthday, whichever came last. The period at risk continued until a breast cancer diagnosis, death, emigration, disappearance, or December 31, 1992 (at which date the cancer registry was considered complete), whichever occurred first. The possible impact of the duration of the pregnancies that ultimately ended as induced abortions was investigated in a log-linear Poisson regression model.[26] Gestational age-specific person-years at risk were calculated in groups for induced abortions that took place at <7, 7 to 8, 9 to 10, 11 to 12, 13 to 14, 15 to 18, and >18 weeks of gestation. Women with more than one induced abortion were in the period between the first and second abortion considered under risk according to the gestational age of the first induced abortion and after the second but before the third according to the gestational age of the second induced abortion, etc. Adjustment was made for attained age in 1-year intervals and calendar period in 5-year intervals, parity (0,1,2,3,4,5,6,7+), and age at first birth (12 to 19, 20 to 24, 25 to 29, 30 to 34, >34). In an exploratory analysis we also categorized calendar time and age at first birth in 1-year intervals but this

had no effect on the results arguing against residual confounding. Age of the woman is denoted age of the woman at diagnosis for clarification. Trend tests were performed treating the grouped gestational age as a continuous variable with each group represented by the mean gestational age. The linear assumption in the trend test was checked by a likelihood ratio test against the model with gestational age as a categorical variable. Estimation of breast cancer incidence rate ratios was performed using the SAS procedure PROC GENMOD.[27] These rate ratios are called relative risks in the following.

Results

Overall, 1,529,512 women were included in the cohort. Of these, 280,965 (18.4 percent) had a total of 370,715 induced abortions distributed as follows: 215,902 women (76.8 percent) had one induced abortion, 47,906 women (17.1 percent) had two, and 17,157 women (6.1 percent) had three or more induced abortions. The gestational age-specific distribution of the number of induced abortions was as follows: <7 weeks: 3.1 percent, 7 to 8 weeks: 37.1 percent, 9 to 10 weeks: 41.9 percent, 11 to 12 weeks: 15.7 percent, >12 weeks: 2.3 percent. Women without induced abortion represented 25,850,000 person-years of follow-up. In this group 8,908 cases of breast cancer were observed. In comparison, women with a history of induced abortion comprised a total of 2,697,000 person-years of follow-up and 1,338 cases of breast cancer.

Overall, the risk of breast cancer in women with induced abortion was not different from that of women without a history of induced abortion after taking into account potential confounding by age, parity, age at first birth, and calendar time (relative risk 1.00; 95 percent confidence interval 0.94 to 1.06).
Table 1 presents in more detail the association between variables related to the abortion history and the risk of breast cancer. Both a "crude" relative risk (adjusted for age, parity, calendar time, and age at first birth) and an adjusted multivariate relative risk (adjusted also for the other variables presented in the table) was calculated. As it appears the adjustment did barely change any of the risk estimates. Although age at the induced abortion did not significantly influence the overall risk, there was a tendency towards higher risks of breast cancer in women who were very young, i.e. between 12 and 19 years of age (relative risk 1.29, 95 percent confidence interval 0.80 to 2.08). Neither the number of induced abortions nor live birth history (induced abortion in a nulliparous or before/after a lifebirth) significantly influenced the breast cancer risk. We also looked at the time interval between the induced abortion and breast cancer diagnosis but found no indication of a differential effect (<1 year: RR=0.97; 1-4 years: RR=0.99; 5+ years: RR=1 (ref.)) (Table 1).

There was no effect modification by age of the women at diagnosis of the association between induced abortion and breast cancer risk (12 to 34 years: RR=0.95 (0.78 to 1.14); 35 to 39 years: RR=0.99 (0.87 to 1.14); 40 to 44 years: RR=1.01 (0.91 to 1.12); 45 to 49 years: RR=1.00; 50+ years: RR=1.03 (0.88 to 1.21), P=0.97). Also, there was no effect modification by calendar period (P=0.17) or by calendar period at induced abortion (P=0.83). However, with each week's increase in gestational age, a 3 percent increase was observed in the risk of breast cancer. The relative risk increased from 0.81 (95 percent confidence

Table 1. Adjusted relative risk of breast cancer in women with a history of induced abortion

Abortion history	No. of cancers	Person-years (thousands)	Relative risk (95% CI)*	Multivariate relative risk (95% CI)†
Wk of gestation				
<7	36	82	0.81 (0.58-1.13)	0.81 (0.58-1.13)
7-8	526	1012	1.01 (0.89-1.14)	1.01 (0.89-1.14)
9-10‡	534	1118	1	1
11-12	205	422	1.12 (0.95-1.31)	1.12 (0.95-1.31)
13-14	6	14	1.13 (0.50-2.52)	1.13 (0.51-2.53)
15-18	17	35	1.24 (0.76-2.01)	1.23 (0.76-2.00)
>18	14	14	1.92 (1.13-3.26)	1.89 (1.11-3.22)
Age at induced abortion (yr)				
12-19	23	458	1.32 (0.82-2.12)	1.29 (0.80-2.08)
20-24‡	68	617	1	1
25-29	161	552	0.91 (0.68-1.20)	0.93 (0.69-1.25)
30-34	366	529	0.99 (0.76-1.29)	1.03 (0.77-1.38)
≥35	720	541	1.04 (0.81-1.34)	1.07 (0.80-1.43)
No. of induced abortions				
1‡	1105	2220	1	1
2	191	376	1.08 (0.92-1.26)	1.09 (0.94-1.28)
≥3	42	101	0.99 (0.73-1.35)	1.02 (0.75-1.40)
Time since induced abortion (yr)				
<1	63	339	0.97 (0.75-1.25)	0.97 (0.75-1.25)
1-4	315	1048	0.99 (0.87-1.12)	0.99 (0.87-1.13)
≥5‡	960	1310	1	1
Time of induced abortion and live-birth history				
Nulliparous women	95	694	1.04 (0.83-1.29)	1.04 (0.83-1.31)
Parous women				
Induced abortion before 1st live birth	77	350	1.08 (0.85-1.36)	1.08 (0.82-1.44)
Induced abortion after 1st live birth‡	1154	1582	1	1
Other§	12	71	0.76 (0.43-1.34)	0.74 (0.41-1.33)

*The relative risks were calculated separately for each of the five variables with adjustment for women's age, calendar period, parity, and age at first birth. CI denotes confidence interval.

†Values were adjusted for women's age, calendar period, parity, age at first birth, and the other variables shown in the table.

‡The women with this characteristic served as the reference group.

§ "Other" denotes induced abortion occuring after delivery of a first child in women who also had induced abortion before delivery of a first child.

interval, 0.58 to 1.13) in women with a gestational age of latest abortion of less than 7 weeks to 1.38 (95 percent confidence interval, 1.00 to 1.90) in women with a gestational age of more than 12 weeks at abortion (P_{trend}= 0.02). We acknowledge the small number of cases in the group above 12 weeks but further evaluated this period and found the following relative risks: weeks 13 to 14: 1.13 (0.51 to 2.53); weeks 15 to 18: 1.23 (0.76 to 2.00); weeks >18: 1.89 (1.11 to 3.22) (P_{trend} =0.016, Table 1).

Discussion

Our population-based cohort study uncovered no overall increased risk of breast cancer in women with a history of induced abortion. This is very much in line with previous retrospective cohort studies.[9,10,15,16] Two of these studies rather suggested a decreased risk.[10,15] However, all previously published retrospective cohort studies have lacked detailed information on gestational length of the abortion. Results from case-control studies have been inconsistent.[6-8,11-14,17-23] Several reports, particularly those focusing on induced abortions, have documented an increased risk.[7,8,13,21-23]

An almost inevitable concern with the results obtained in these case-control studies is the potential problem with differential misclassification. Even after legislation of abortion the issue continues to be sensitive and it is most likely that women with serious diseases such as breast cancer report induced abortions more completely than other women. Based on a Swedish study which compared registry information with interview data regarding induced abortion, an increase in risk of breast cancer of between 16 and 50 percent could be attributed to differential misclassification in interview data.[28,7] The concern with reporting misclassification led Newcomb et al. to conclude that studies which do not rely on interviews with cases and controls are necessary to resolve the issue adequately.[8] In the present study, all information both with respect to dates and number of induced abortions, reproductive history, and cancer diagnoses was obtained from national registries with mandatory reporting covering the entire population. Follow-up included complete knowledge on death and emigration and was performed through computerized linkage of registry information by means of person-identifiable registration numbers. We therefore conclude that some of the major methodological problems in previous studies were overcome in the present study.

A limitation of our research database was that information on induced abortions was only computerized since 1973. Therefore, for some of the oldest women in the cohort we might have obtained an incomplete history of induced abortions. However, according to the present data, women with a history of induced abortion did not experience a risk of breast cancer different from that of women without such a history. Furthermore, we did not find any indication that the number of induced abortions had any bearing on the breast cancer risk. Therefore, we consider it very unlikely that missing information about abortions prior to 1973 should have any influence on the results of our analysis.

Whereas induced abortion had no overall effect on the risk of breast cancer, we documented a significantly increasing risk with increasing gestational age of the abortion. The fact that such an increase did not affect the overall result of no association clearly indicates that it is based on small numbers and as such should be

considered with caution. We have no explanation as to why a very early induced abortion was associated with a slightly, although insignificant, risk decrease. However, the significantly increasing trend was also apparent after excluding this category of the very early induced abortions. The increased risk in second trimester abortions find biological support from rat experiments and is in line with the hypothesis by Russo.[3]

We were concerned that women who were diagnosed with breast cancer during pregnancy would be advised to have an induced abortion and that this situation would not be equally distributed by gestational age of the abortion. However, the time at risk was only calculated up to the diagnosis of breast cancer in the study, and therefore only later occurring induced abortions that were misclassified as occurring prior to the cancer diagnosis could represent a potential problem. However, a stratified analysis of the risk of breast cancer according to time since induced abortion showed no differential risk and in particular no increased risk within the first year after abortion.

Induced abortions taking place at a gestational age of more than 12 weeks were primarily performed on medical or social indications. This group of women could have a higher breast cancer risk which might explain the elevated relative risks observed for women with late induced abortions. However, we are not aware of any medical condition associated with both a high breast cancer risk and with late induced abortion. We specifically tested whether women with a diagnosed trisomy 21 pregnancy, who also tend to be commonly found among those having a late induced abortion, should have an increased risk of breast cancer. Based on a cohort study of 1335 mothers with this condition (16,022 person-years of follow-up) we found no increased breast cancer risk in this group compared to other parous women (data not shown). It is possible that women with drinking problems delay the interruption of an unwanted pregnancy. Thus, alcohol intake has been associated with increased breast cancer risk but the associations have been weak and inconsistent.[29] Another social indication for late induced abortion would, if anything, tend to yield an overrepresentation of women of low socio-economic status. However, breast cancer risk is associated with high social status and thus we would expect the observed relative risks to be underestimated rather than the opposite.

Nulliparous women with a history of induced abortion did not differ from parous women in risk of breast cancer. In the group of nulliparous women it is irrelevant to consider confounding by lactation and effect of later births. We are therefore very confident that neither of these variables had any confounding potential that influenced our overall result.

Study 2. Time since childbirth and prognosis in primary breast cancer

Material and methods

The Danish Breast Cancer Cooperative Group, DBCG, started its national prospective studies in 1977. Up till now three treatment programs have been in function, DBCG 77 (patient accrual from 1978-1982), DBCG 82 (patient accrual from 1983-1989), and DBCG 89 (ongoing accrual started 1990). The Danish Can-

cer Registry contains information on close to all incident cases of malignant neoplasms diagnosed in Denmark since 1943 [8]. DBCG has information on 93 percent of all breast cancer patients aged less than 45 years at diagnosis reported to The Danish Cancer Registry.

The primary surgical treatment of the patients included total mastectomy plus axillary sampling (90 percent of the population), or lumpectomy with axillary sampling. Patients were hereafter classified as either low-risk or high-risk according to histopathological criteria. Low-risk patients had tumours ≤ 5 centimetres in diameter without axillary lymph node metastases and without invasion into the skin or the deep resection line (DBCG 77 and DBCG 82). In the DBCG 89 program, premenopausal node negative patients in addition were required to have tumours classified as histologic grade I. High-risk patients were those with a primary tumour > 5 centimetres or with lymph node metastases in the axilla or with tumour growth into the skin or the deep resection line (DBCG 77 and DBCG 82). In the DBCG 89 program premenopausal patients with grade II and III of anaplasia were classified as high-risk patients. Patients with bilateral breast cancer, distant metastases, inflammatory cancer, with contraindication to the planned postoperative therapy, or patients who were not treated according to the surgical guidelines were not allocated to treatment protocols (miscellaneous group). The miscellaneous patient group could be separated into a group with a favourable prognosis and a group with a bad prognosis. The patients who were not treated according to surgical guidelines had an overall good prognosis compared with patients excluded for other reasons. In all three programs low-risk patients were given no systemic treatment after surgery. In the DBCG 77 program, high-risk patients were allocated to either postoperative radiotherapy or radiotherapy and systemic therapy as it has been described elsewhere [9]. In the DBCG 82 program, high-risk patients were allocated to systemic therapy and radiotherapy or to systemic therapy alone [9]. The target for radiotherapy following mastectomy included the chest wall and regional lymph nodes (axillary, supra-/infra clavicular, and parasternal nodes). In the DBCG 89 programme, high-risk patients were given systemic therapy according to the steroid hormone receptor status. Radiotherapy including the chest wall was given if the tumour invaded the deep resection line. All tumourectomized patients were given radiotherapy to the residual breast tissue.

Since 1968, the Civil Registration System (CRS) has assigned a unique 10-digit identification number to all residents in Denmark that permits accurate linkage of information from different registries. The CRS-registry also keeps updated files on dates of childbirths and vital status. Information about stillbirths was added from the National Birth Registry.

Permission was obtained in advance from the National Scientific Ethics Committee and the Data Protection Board to link information on patients in the DBCG-registry with the CRS-registry. Women born before 1935 have no systematic link to all their children in the CRS- registry. Therefore, to obtain complete reproductive history of the women we restricted our study group to those born since 1st. April 1935. Because our objective was to study the influence of time since birth on breast cancer survival and we furthermore wanted to limit the analysis to pre-

menopausal women, we only included women aged 45 years or less at the time of their breast cancer diagnosis. All women diagnosed before 1st. October 1994, were included and followed until 1st. October 1995, with respect to vital status.

The associations between the study variables and survival were investigated using the Cox Proportional Hazards method [10]. Multivariate analyses included tumour characteristics, time between diagnosis and most recent previous childbirth, parity at diagnosis, age at diagnosis, year of treatment, and protocol allocation. Parity was eliminated from the final multivariate model as it was not significant. Based on the finding of a rather constant survival for the age categories representing six and more years after childbirth we defined a reference category for the variable "time since birth" as six+ years to be used in the multivariate analyses (Table 2). The adequacy of the proportional hazard assumptions for the included variables was checked by log(-log)plots from stratified multivariate analyses. The Cox-regression was performed in four strata (information on tumour size and lymph node status available, only tumour size missing, only lymph node status missing, both missing). Estimation was done using the SAS procedure PROC PHREG [11].

Results

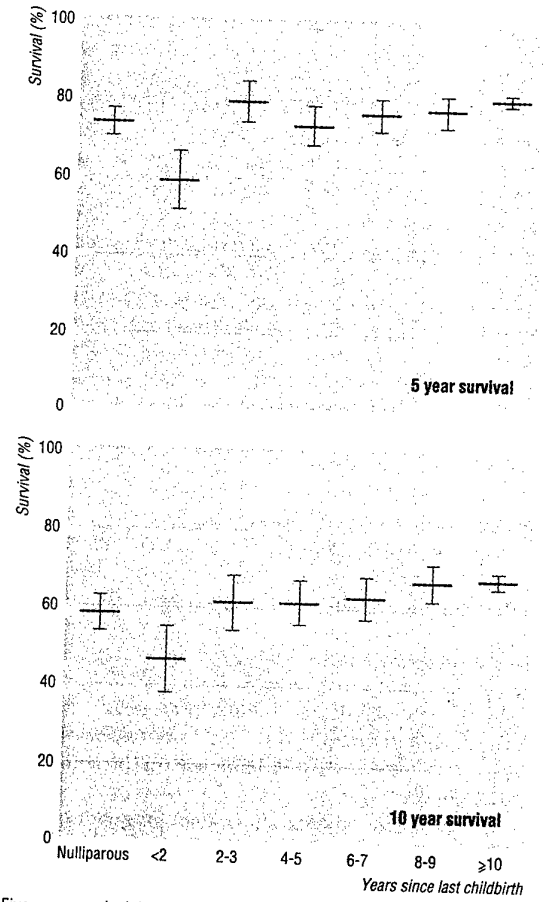
Overall, 5,752 women aged 45 years or less were identified for this particular study. The influence of pregnancy subsequent to treatment of breast cancer is unknown [12], and hence 100 patients were excluded due to delivery after the time of their diagnosis, leaving 5,652 patients for further analyses. The follow-up time ranged from 13 months to 17 years representing a total of 34,130 person-years of follow-up. Overall, 4,957 women (87.7 percent) were parous and 695 women (12.3 percent) were nulliparous. The distribution of patient age, tumour characteristics, and risk group allocation according to time since last birth is given in Table 1.

Figure 1 (and Table 4) illustrates the overall 5 and 10-year survival for women according to time since birth. Women diagnosed less than two years after having given birth had a crude 5-year survival of 58.7 percent and a 10-year survival of 46.1 percent, compared with 78.4 percent (5-year) and 66.0 percent (10-year), respectively, for women who had their last delivery more than two years prior to their cancer diagnosis. Recent pregnancy conferred a negative effect both on patients who received adjuvant treatment and those who did not. Women with a recent birth (< 2 years) who were classified with low-risk breast cancer and as such did not receive adjuvant systemic treatment, had a crude survival of 75.0 percent (5-year) and 55.6 percent (10-year), respectively, compared with 88.5 percent (5-year) and 77.8 percent (10-year) for women whose last child birth was more than two years prior to their diagnosis. Women classified with high-risk disease, receiving adjuvant treatment, had a crude survival of 53.2 percent (5-year) and 41.2 percent (10-year), respectively, compared with 72.0 percent (5-year) and 58.2 percent (10-year) for women whose last child birth was more than two years prior to their diagnosis.

The effect of time since birth was further evaluated for parous women in a multivariate analysis that considered the influence of age at diagnosis, tumour size at

diagnosis, numbers of positive axillary lymph nodes, grade of anaplasia, protocol allocation, year of treatment, and number of full-term pregnancies. As shown in Table 2, the prognosis remained significantly worse for women who gave birth to a child within the past two years (relative risk: 1.58 (95 percent confidence interval: 1.24-2.02) compared with women who had given birth six or more years ago (p=0.0002). The increased risk associated with a recent birth was found to be 2.1-fold in the first year and 1.3-fold in the second year.

In order to investigate whether the negative effect of a recent birth was modified by age at diagnosis, stage of disease (measured by number of positive axillary lymph nodes), or tumour size, we performed a stratified analysis that adjusted for all other considered factors as given above (Table 3). Neither age at diagnosis, nodal status, nor tumour size had any significant modifying effect on the poor survival for the group of women with a history of a recent birth (< 2 years).



Five year survival (top) and 10 year survival (bottom) according to time since last childbirth in 5652 women with primary breast cancer. Bars indicate 95% confidence intervals

Table 1. Distribution of 5,652 breast cancer patients 45 years or less at diagnosis according to tumour characteristics, age, risk group allocation, and time since birth.

	Time since birth n (%)				
	Nulliparous	< 2 years	2-3 years	4-5 years	6 years
Total No	695	201	280	349	4127
Age					
<30 years	46 (6.6)	33 (16.4)	24 (8.6)	16 (4.6)	4 (0.1)
30-39 years	261 (37.6)	144 (71.6)	211 (75.4)	224 (64.2)	1157 (28.0)
40-45 years	388 (55.8)	24 (11.9)	45 (16.1)	109 (31.2)	2966 (71.9)
Tumour size					
2 cm	299 (43.0)	94 (46.8)	134 (47.9)	167 (47.9)	2240 (54.3)
>2. 5 cm	260 (37.4)	74 (36.8)	94 (33.6)	115 (33.0)	1308 (31.7)
> 5 cm	72 (10.4)	14 (7.0)	33 (11.8)	33 (9.5)	266 (6.5)
No information	64 (9.2)	19 (9.5)	19 (6.8)	34 (9.7)	313 (7.6)
Positive nodes					
0	328 (47.2)	81 (40.3)	129 (46.1)	153 (43.8)	2180 (52.8)
1-3	200 (28.8)	56 (27.9)	86 (30.7)	115 (33.0)	1134 (27.5)
4-9	85 (12.2)	34 (16.9)	33 (11.8)	44 (12.6)	449 (10.9)
10	24 (3.5)	18 (9.0)	10 (3.6)	17 (4.9)	135 (3.3)
No information	58 (8.4)	12 (6.0)	22 (7.9)	20 (5.7)	229 (5.6)
Histologic grading					
I	146 (21.0)	30 (14.9)	52 (18.6)	71 (20.3)	994 (24.1)
II + III	394 (56.7)	132 (65.7)	166 (59.3)	205 (58.7)	2219 (53.8)
ND*	155 (22.3)	39 (19.4)	62 (22.1)	73 (20.9)	914 (22.2)
Protocol allocation					
Yes	523 (75.3)	156 (77.6)	228 (81.4)	289 (82.8)	3442 (83.4)
No					
Not treated according to surgical guidelines	100 (14.4)	35 (17.4)	42 (15.0)	44 (12.6)	521 (12.6)
Not allocated due to other reasons†	72 (10.4)	10 (5.0)	10 (3.6)	16 (4.6)	164 (4.0)

*Including patients with non-ductal carcinomas and patients without information on histologic grading

†Medical contraindications, bilateral breast cancer, distant metastasis, or inflamatory cancer.

Table 2. Adjusted relative risk (aRR) of dying according to prognostic factors, age at diagnosis, and time since birth among 4,957 parous breast cancer patients 45 years or less.

Variables	aRR (95% CI)*
Age at diagnosis	
<30 years	1.0 ref.
30-39 years	0.88 (0.62-1.27)
40-45 years	0.80 (0.55-1.16)
Tumour size	
2 cm	1.0 ref.
>2. 5 cm	1.67 (1.48-1.89)
> 5 cm	2.44 (2.03-2.92)
Positive nodes	
0	1.0 ref.
1-3	1.58 (1.39-1.81)
4-9	3.04 (2.61-3.54)
10	3.90 (3.12-4.87)
Histologic grading	
I	1.0 ref.
II + III	2.27 (1.93-2.67)
ND†	1.26 (1.04-1.54)
Time since birth	
< 2 years	1.64 (1.28-2.09)
2-3 years	1.00 (0.80-1.26)
4-5 years	1.20 (0.98-1.46)
6 years	1.0 ref.

*Adjusted relative risk (95% confidence intervals) adjusted for the other characteristics listed above and overall parity, age at first birth, year of treatment, and protocol allocation.

†Patients with non-ductal carcinomas.

Table 3. Adjusted relative risk, aRR (95% confidence interval) of dying according to age at diagnosis, nodal status, tumour size, and time since birth among 4,957 parous breast cancer patients 45 years or less.

	Time since birth			
	< 2 years	2-3 years	4-5 years	6 years
	aRR	aRR	aRR	aRR
Age at diagnosis†				
33 years	1.6 (1.2-2.3)*	1.1 (0.8-1.6)	1.2 (0.8-1.9)	1.0 ref.
> 34 years	1.7 (1.2-2.3)*	0.9 (0.7-1.2)	1.2 (1.0-1.5)	1.0 ref.
Tumour size				
2 cm	1.7 (1.1-2.4)*	1.4 (1.0-2.0)	1.4 (1.0-1.9)	1.0 ref.
> 2 cm	1.5 (1.1-2.0)*	0.8 (0.6-1.1)	1.0 (0.8-1.4)	1.0 ref.
Nodal status				
Negative	1.6 (1.0-2.4)*	1.1 (0.8-1.7)	1.0 (0.7-1.4)	1.0 ref.
Positive	1.5 (1.1-2.0)*	1.0 (0.7-1.3)	1.3 (1.1-1.7)*	1.0 ref.

*$p<0.05$

†Patients separated into two groups according to median age among patients with child birth less than two years before diagnosis.

Table 4. Number of primary breast cancer patients under 45 years of age (N=5,652). Five and ten-year survival according to time since birth. Denmark 1977 - 1994.

Time since birth	N	5-year survival	10-year survival
Nulliparous	695	73.1 (69.5-76.7)	57.7 (53.0-62.5)
< 2 year	201	58.7 (51.2-66.1)	46.1 (37.5-54.6)
2-3 years	280	78.8 (73.7-83.9)	60.8 (53.8-67.8)
4-5 years	349	72.8 (67.8-77.7)	61.1 (55.3-66.9)
6-7 years	448	75.8 (71.5-80.0)	62.6 (57.3-67.8)
8-9 years	526	77.0 (73.2-80.8)	66.9 (62.3-71.4)
10 years	3,153	79.6 (78.0-81.1)	67.3 (65.2-69.3)

Discussion

We documented a particularly poor survival for women who were diagnosed with a breast cancer within two years after having given birth. This finding was obtained using a large and very complete population-based database with detailed information on tumour characteristics, treatment regimes, reproductive factors, and vital status. The adverse effect on the prognosis was observed irrespective of the

woman s age, the size of the tumour, and the stage of the disease. In a small multi-center study involving nine centres and a total of 152 young mothers (<30 years) with breast cancer, Guinee et al. [6] found an increased mortality in women who gave birth up to four years prior to their diagnosis. Other studies indicate that breast cancer diagnosed during lactation is associated with poor survival [13,14]. However, a recent study by von Schoultz and colleagues [7] failed to support such an association. A limitation in all these studies has been their sample size. Furthermore, they have generally been unable to adequately adjust for confounders such as other reproductive history, tumour size, axillary lymph node status, and histological grading.

To diagnose a breast cancer among young women in general and in pregnant women and lactating women in particular are difficult due to the density of the mammary glands. This is reflected in a significant diagnostic delay among these patients [12,15]. In the present study there was a tendency for recently pregnant women to be classified with more advanced disease that, at least to some extent, could be caused by delayed diagnosing. However, our detailed information on each woman s tumour characteristics allowed us to adjust for this phenomenon thoroughly. Thus, independent of the influence caused by delayed diagnosis, women with a recent birth prior to their diagnosis conferred an increased risk of dying of about 60 percent compared to other women with breast cancer.

Breastfeeding was earlier considered to influence the risk of breast cancer development but most recent evidence suggests that there be no important overall association [19]. Whether breastfeeding should influence the prognosis of the disease is unknown but the lack of effect on the risk of disease does not necessarily strengthen a possible effect on its prognosis. In our study, we did not have information on breast feeding. Lactating women entails a very different hormonal enviroment to that of non-lactating post partum women, which makes the group of women with recent pregnancy heterogenous. However, we note that a poor survival was observed also in the second year after birth, at which time most women have stopped breastfeeding.

Experimental data support that pregnancy may confer a growth-enhancing effect on tumour cells [20]. However, a simple growth-enhancing effect would tend to increase the volume of the tumour at time of diagnosis shortly after pregnancy. We find that the negative effect of a recent birth remains present also after having taken into account factors that reflect the volume of the tumour, i. e. tumour size and nodal status (Table 3). Therefore, we suggest that the most likely explanation for our finding is that the pregnancy changes the course of the disease by increasing the risk of a highly malignant growth-pattern of already existing tumour cells.

It has long been known that early age at first full-term pregnancy is associated with a low risk of breast cancer *development,* whereas women aged 35 years or more at first child birth are at a particularly high risk [1]. In our study, neither tumour size, nodal status, nor age modified the specific *prognostic* effect of recent last delivery. Because breast cancer is rare before the age of 30 years [21], the like-

lihood of giving birth close to the development of a breast cancer diagnosis is significantly larger for women who have their children at an advanced age. Therefore, the adverse influence of pregnancy on breast cancer survival will naturally have the greatest impact in modern societies where women are postponing the time of childbearing to higher ages.

The negative effect of recent pregnancy was pronounced both in the group of women who did not receive adjuvant treatment (low risk group) as well as among patients who all received adjuvant therapy (high risk group). However, it is unknown whether more intensive adjuvant treatment will change the course of the disease in this group of patients. These new findings need be considered while counselling such patients and furthermore be taken into account when the decision of adjuvant treatment is made. We therefore recommend that pregnancy history be recorded at admission of premenopausal breast cancer patients. Furthermore we recommend that such information be recorded in future prospective clinical trials in order for response to adjuvant treatment according to time since last childbirth to be assessed.

Study 3. Parity, age at first childbirth and the prognosis of breast cancer

Materials and methods

We used the DBCG register as described in detail in study 2.

Information on reproductive history was obtained by linkage with the Civil Registration System (CRS). The CRS was established on 1 April 1968 where all residents in Denmark were registered and assigned a unique identification number that permits identity secure linkage of information between registries. Parents were recorded with a link to most of their children born in the beginning of the 1950´s or later and alive in 1968. Since then, the CRS registry has kept updated files on dates on all live-births and residents in Denmark including updated files on vital status. A more detailed description of the reproductive information included in this registry is given elsewhere (Melbye *et al.,* 1997). - Information on stillbirths was available during the period 1978-1993 from the National Birth Registry.

Permission was obtained in advance from the National Scientific Ethics Committee and the Data Protection Board to link information on patients in the DBCG registry with the CRS registry, and the National Birth Registry. Women born before 1935 have no systematic link to all their children in the CRS registry. Therefore, we restricted our study group to women born since 1th. April 1935. All women with a diagnosis of breast cancer before 1th. October 1994, were included and followed until 1th. October 1995, with respect to vital status.

The associations between the study variables and survival were investigated using the Cox Proportional Hazards method (Cox, 1972). Multivariate analyses included tumour size (2 cm, >2 and up till 5 cm, >5 cm), positive lymphnodes (0,1-3,4-9, 10), histological grading (I, II-III, non-ductal patients and those without information on histological grading), age at first birth (nulliparous, <20, 20-24,25-29, 30 years), parity at diagnosis (0,1,2,3, 4), age at diagnosis (<35, 35-39,40-44,45-49,

50 years), year of diagnosis (1977-81,82-87,88-94), and protocol allocation (see table 1). The adequacy of the proportional hazard assumptions for the included variables was checked by log(-logS) plots from stratified multivariate analyses. For both tumour size and lymph node status the hazard rate of the heterogeneous category of missing information was not proportional to the hazard rates of the other categories. Therefore, the Cox-regression was performed in four strata (information on tumour size and lymph node status available, only tumour size missing, only lymph node status missing, both missing). The estimates were only slightly changed if women with missing tumour size or nodal status were excluded from the analysis. Tests for effect modification were performed as tests for interaction between categorized variables. In an exploratory analysis we categorized year of treatment in one-year intervals, but this did not affect the results - a finding that argues against residual confounding. All analyses were performed using likelihood ratio tests by means of the SAS procedure PROC PHREG (SAS Institute Inc., 1992).

Results

By the first of October 1994, 10,803 women with primary breast cancer born after April 1, 1935, were registered in the DBCG. One hundred patients were excluded due to delivery after the time of diagnosis. 1,260 patients (11.8%) were nulliparous, and 9,443 patients (88.2%) were parous. The follow-up time ranged from 13 months to 17 years representing a total of 60,322 person-years of follow-up. Distribution of patients according to age at diagnosis, tumour characteristics, protocol allocation, parity, and age at first birth is given in table 1. The influence of these factors on breast cancer prognosis were evaluated in a multivariate analysis. The relative risk of dying according to tumour characteristics and status as nulliparous or parous is given in table 2. Table 3 presents the relative risk of dying according to parity and age at first childbirth in parous women. Parous women were found to have a minor insignificantly reduced risk of dying compared with nulliparous women (relative risk: 0.95; 95% confidence interval: 0.86-1.06). The prognosis was unaffected by the number of children in the group of parous women (p=0.78, table 3).

The adjusted relative risk of dying varied significantly according to age at first birth as shown in table 3 (p=0.005). Women having their first child at the age of 25 - 29 years had the best prognosis. The relative risk of dying was significantly reduced for women having there first child between the age of 20 years to 24 years (RR: 0.88, 95% CI: 0.78-0.99) and women with primary childbirth between the age of 25 years to 29 years (RR: 0.80, 95% CI: 0.70-0.91) compared with women having primary childbirth below the age of 20 years (reference group). To investigate whether the prognostic effect of age at first birth was modified by age at diagnosis, extend of disease (measured by number of positive axillary lymph nodes), or tumour size, we tested for effect modification with adjustment for all other considered factors as given above (Table 4). Neither tumour size (p=0.63) nor nodal status (p=0.74) had a significantly modifying effect on the prognostic influence of age at first birth. There was a trend towards the prognostic effect of age at first childbirth being more pronounced among women diagnosed between the age of 40 to 50 years. However, this finding was not significant (p=0.27).

Oestrogen receptor (ER) status was available on 6,016 patients. Sixty-nine percent were classified as ER positive and 31% were classified as ER negative. The negative prognostic effect of age at first childbirth was not affected by ER status.

Table 1. Distribution of 10,703 women with primary breast cancer born after April 1, 1935, diagnosed during 1978-1994 according to age at diagnosis, tumour characteristics, protocol allocation, parity, and age at first childbirth.

	Age at first birth n (%)				
	Nulliparous	< 20 years	20-24 years	25-29 years	30 years
Total No	1,260	1,468	4,416	2,670	889
Age at diagnosis					
< 35 years	138 (11.0)	71 (4.8)	225 (5.1)	184 (6.9)	31 (3.5)
35-39 years	169 (13.4)	211 (14.4)	595 (13.5)	374 (14.0)	122 (13.7)
40-44 years	318 (25.2)	434 (29.6)	1,128 (25.5)	701 (26.3)	258 (29.0)
45-49 years	337 (26.8)	452 (30.8)	1,392 (31.5)	781 (29.3)	273 (30.7)
50 years	298 (23.7)	300 (20.4)	1,076 (24.4)	630 (23.6)	205 (23.1)
Tumour size					
2 cm	576 (45.7)	837 (57.0)	2,446 (55.4)	1,429 (53.5)	461 (51.9)
>2, 5 cm	480 (38.1)	457 (31.1)	1,477 (33.5)	936 (35.1)	300 (33.7)
> 5 cm	119 (9.4)	87 (5.9)	261 (5.9)	158 (5.9)	76 (8.5)
No information	85 (6.8)	87 (5.9)	232 (5.3)	147 (5.5)	52 (5.8)
Positive nodes					
0	600 (47.6)	784 (53.4)	2,301 (52.1)	1,359 (50.9)	448 (50.4)
1-3	374 (29.7)	401 (27.3)	1,204 (27.3)	777 (29.1)	237 (26.7)
4-9	152 (12.1)	160 (10.9)	538 (12.2)	307 (11.5)	127 (14.3)
10	49 (3.9)	48 (3.3)	165 (3.7)	110 (4.1)	39 (4.4)
No information	85 (6.8)	75 (5.1)	208 (4.7)	117 (4.4)	38 (4.3)
Histologic grading					
I	302 (24.0)	362 (24.7)	1,135 (25.7)	668 (25.0)	210 (23.6)
II + III	664 (52.7)	802 (54.6)	2,268 (51.4)	1,353 (50.7)	471 (53.0)
ND[a]	294 (23.3)	304 (20.7)	1,013 (22.9)	649 (24.3)	208 (23.4)
Protocol allocation					
Yes	980 (77.8)	1,234 (84.1)	3,748 (84.9)	2,245 (84.1)	740 (83.2)
No					
Not treated according to surgical guidelines	158 (12.5)	168 (11.4)	457 (10.4)	291 (10.9)	101 (11.4)
Not allocated due to other reasons[b]	122 (9.7)	66 (4.5)	211 (4.8)	134 (5.0)	48 (5.4)
Parity	-				
1		157 (10.7)	586 (13.3)	648 (24.3)	489 (55.0)
2		639 (43.5)	2,325 (52.7)	1,555 (58.2)	350 (39.4)
3		471 (32.1)	1,199 (27.2)	399 (14.9)	42 (4.7)
4		201 (13.7)	306 (6.9)	68 (2.6)	8 (0.9)

[a] Including patients with non-ductal carcinomas (n=2089, 84.6%) and patients without information on histologic grading (n=379, 15.4%). [b] Medical contraindications, bilateral breast cancer, distant metastasis, or inflamatory cancer.

Table 2. Adjusted relative risk (aRR) of dying according to prognostic factors, protocol allocation, and parity, in 10,703 breast cancer patients born after April 1, 1935, and diagnosed 1978-1994.

Variables	aRR (95% CI)[a]
Tumour size	
2 cm	1 ref.
>2, 5 cm	1.63 (1.49-1.78)[b]
> 5 cm	2.17 (1.90-2.49)[b]
Positive nodes	
0	1 ref.
1-3	1.71 (1.53-1.91)[b]
4-9	3.32 (2.97-3.72)[b]
10	4.72 (4.02-5.52)[b]
Histologic grading	
I	1 ref.
II + III	2.33 (2.07-2.62)[b]
ND[c]	1.18 (1.02-1.36)[b]
Protocol allocation	
Allocated patients	1 ref
Not treated according to guidelines	1.04 (0.91-1.17)
Not allocated due to other reasons[d]	2.76 (2.43-3.13)[b]
Parity	
Nulliparous	1 ref.
Parous	0.95 (0.85-1.06)

[a]Adjusted relative risk (95% confidence intervals) adjusted for all characteristics listed above and age at diagnosis and year of diagnosis.[b]$p<0.05$. [c]Patients with non-ductal carcinomas and patients without information on histologic grading. [d]Medical contraindications, bilateral breast cancer, distant metastasis, or inflamatory cancer.

Table 3. Adjusted relative risk (aRR) of dying according to number of full-term pregnancies, and age at first childbirth in 9,443 parous breast cancer patients born after April 1, 1935, and diagnosed 1978-1994.

Variables	aRR (95% CI)[a]	aRR (95% CI)[b]
Parity		
Nulliparous	1.04 (0.90-1.19)	
1	1 ref.	1 ref.
2	0.96 (0.86-1.07)	0.97 (0.86-1.08)
3	0.99 (0.88-1.12)	0.98 (0.85-1.11)
4	1.07 (0.90-1.28)	1.04 (0.87-1.25)
Age at first birth		
Nulliparous	0.92 (0.80-1.06)	
< 20 years	1 ref.	1 ref.
20-24 years	0.87 (0.78-0.98)[c]	0.88 (0.78-0.99)[c]
25-29 years	0.79 (0.70-0.90)[c]	0.80 (0.70-0.91)[c]
30 years	0.94 (0.80-1.11)	0.94 (0.79-1.12)

[a] Adjusted relative risk (95% confidence intervals) adjusted for age at diagnosis, tumour size, nodal status histologic grading, protocol allocation, and year of diagnosis. [b] Adjusted relative risk further adjusted for parity factors listed above [c] $p < 0.05$

Table 4. Stratified analysis of risk of dying according to age at diagnosis, nodal status, tumour size, and age at first childbirth among 9,443 parous breast cancer patients.

	Age at first birth < 20 years	20-24 years	25-29 years	30 years
	aRR[a]	aRR[a]	aRR[a]	aRR[a]
Age at diagnosis				
<35 years	1 ref.	1.6 (0.99-2.5)	1.2 (0.8-2.0)	2.0 (0.96-4.1)
35-39 years	1 ref.	0.9 (0.7-1.1)	0.9 (0.7-1.2)	1.1 (0.8-1.6)
40-44 years	1 ref.	0.7 (0.6-0.9)[b]	0.7 (0.6-0.9)[b]	0.8 (0.6-1.0)
45-49 years	1 ref.	0.8 (0.6-1.0)	0.7 (0.6-0.9)[b]	0.9 (0.7-1.2)
50 years	1 ref.	1.1 (0.8-1.5)	0.9 (0.6-1.3)	1.0 (0.6-1.5)
Tumour size				
2 cm	1 ref.	0.8 (0.6-0.9)[b]	0.8 (0.6-0.9)[b]	0.9 (0.7-1.2)
> 2 cm	1 ref.	0.9 (0.7-1.0)	0.8 (0.7-0.9)[b]	0.9 (0.7-1.1)
Nodal status				
Negative	1 ref.	0.8 (0.7-1.0)	0.8 (0.6-0.97)[b]	1.0 (0.7-1.3)
Positive	1 ref.	0.9 (0.8-1.0)	0.8 (0.7-0.9)[b]	0.9 (0.8-1.1)

[a]Adjusted relative risk (95% confidence intervals) adjusted for age at diagnosis, tumour size, nodal status histologic grading, protocol allocation, and year of diagnosis. [b]$p<0.05$

We found strong evidence that young age at first birth is associated with poor survival of breast cancer, despite its protective effect on breast cancer development. Although some studies have not supported this observation (Ewertz *et al.,* 1991; Lees *et al.,* 1989; Mohle Boetani *et al.,* 1988), there is accumulating evidence that supports it (Schouten *et al.,* 1997; Kogevinas, 1990; Greenberg *et al.,* 1985). A limitation of previous studies has been their small sample sizes (range 582-1,744 subjects) compared with the present study. Furthermore, these studies have primarily been based on retrospectively collected information obtained among cases and controls through interviews. The present population-based study was based on prospectively collected data, with detailed exposure and outcome information that limits possibilities for recall bias.

Previous reports have shown the risk of developing breast cancer to be reduced among women who have their first child at an early age (MacMahon *et al.,* 1970; Ewertz *et al.,* 1990). Based on a large cohort of 1.5 million women and including more than 10,000 breast cancer cases we have similarly found a strongly increasing risk of breast cancer with increasing age at first childbirth (Wohlfahrt et al., unpublished). Thus, one could argue that some women who avoided breast cancer because of a delivery at an early age would have developed breast cancer if they had their primary childbirth late or if they had remained nulliparous. These avoided breast cancers might be those with the most favourable course. Following this argument the observed reduced survival in breast cancer patients with early first

childbirth might reflect a selection of more aggressive cases rather than a direct biologic effect of the early pregnancy on the carcinogenic process. We acknowledge that women with an early first childbirth did not have a poorer profile of the available prognostic factors. However, these prognostic factors do not necessarily offer a complete picture of the biological behaviour of the tumours.

There was an indication, although not being significant, that early first childbirth primarily served as a negative prognostic indicator of breast cancer in older premenopausal women aged 40 to 49 years. The assumption that the negative effect of early first childbirth is a consequence of a selection is supported by epidemiologic data showing that the protective effect of early first childbirth on breast cancer development is most pronounced in older premenopausal women (Ewertz *et al.,* 1990). In the western world the median age of first childbirth has increased over the past decades. It is generally accepted that this postponement of motherhood has contributed to the rising incidence of breast cancer. Our study suggests that the postponement of motherhood might have a beneficial effect on overall breast cancer prognosis.

Studies on overall parity as a prognostic factor have been contradictory (von Schoultz *et al.,* 1995; Palmer *et al.,* 1982; Guinee *et al.,* 1994; Mason *et al.,* 1990; Lees *et al.,* 1989; Lehrer *et al.,* 1992; Wang *et al.,* 1985; Orr and Fraher, 1995; Mohle Boetani *et al.,* 1988; Korzeniowski and Dyba, 1994; Black *et al.,* 1983; Papatestas *et al.,* 1980). We have previously found that pregnancy within two years before a diagnosis of breast cancer was associated with reduced survival (Kroman *et al.,* 1997). This combined with the present observation of early first childbirth being a negative prognostic factor could explain the finding reported by some researchers of an association between high parity and poor prognoses (Wang *et al.,* 1985; Lees *et al.,* 1989; Korzeniowski and Dyba, 1994). Women with high parity would be expected to have their first child early and have their last child late. Therefore, women with high parity would be overrepresentated in the two high-risk groups defined by us. In the present study high parity alone did not serve as an independent prognostic factor.

The observation that breast cancer may be a high social status disease has been related to differences in childbirth patterns (Kelsey and Horn Ross, 1993). In contrast, several studies have shown that low social class is associated with reduced survival (Gordon *et al.,* 1992; Karjalainen and Pukkala, 1990; Kogevinas *et al.,* 1991). It may be of relevance for the latter finding that poorly educated women tend to have their first child earlier than women with higher education level (Knudsen, 1993).

Study 4. Should women be advised against pregnancy after breast-cancer treatment?

Material and methods

We used information from the DBCG register as described in detail in study 2.

Patients with bilateral breast cancer, distant metastases, inflammatory cancer, with contraindication to the planned postoperative therapy, or patients who were not

treated according to the surgical guidelines were not allocated to treatment protocols (miscellaneous group). The miscellaneous patient group could be separated into a group with favourable prognosis and a group with poor prognosis. Patients who were not treated according to surgical guidelines had an overall good prognosis compared with patients excluded for other reasons.

The Danish Civil Registration System (CRS) was established in 1968 and since then a unique identification number has been assigned to all residents in Denmark. Individual information is kept under the personal identification number in all national registers permitting accurate linkage of information between these registries. The CRS registry keeps updated files on vital status and dates of childbirths with a systematic link to the children of women born after April 1, 1935. A detailed description of the information included in this registry is given elsewhere [20,21]. Information on stillbirths after 1977 and induced abortions after 1973, including gestational age of the foetus, was available from the National Birth Registry and the National Induced Abortion registry.

Permission to perform the study was obtained in advance from the National Scientific Ethics Committee and the Data Protection Board. Information on patients in the DBCG registry was linked with the other national registries to obtain information on pregnancy history and vital status. As women born before 1935 have no systematic link to all their children in the CRS registry, we restricted our study group to women born since April 1, 1935. Since the aim was to identify women with pregnancies, we further restricted the study group to women aged 45 years or less at the time of diagnosis. All women diagnosed before October 1, 1994, were included and followed until October 1, 1995, with respect to vital status.

The associations between the study variables and survival were investigated using the Cox Proportional Hazards method. Multivariate analyses included tumour characteristics, time between diagnosis and most recent previous childbirth (with nulliparous in a separate category), age at diagnosis, year of treatment, protocol allocation, full-term pregnancy after diagnosis, induced abortion after diagnosis, and spontaneous abortion after diagnosis. The three last variables were included in the analysis as time-dependent variables. The adequacy of the proportional hazard assumptions for the included variables was checked by log(-log)S-plots from stratified multivariate analyses. For both tumour size and lymph node status, the hazard rate of the heterogeneous category of missing information was not proportional to the hazard rates of the other categories. Therefore, the Cox regression was performed in four strata (information on tumour size and lymph node status available, only tumour size missing, only lymph node status missing, both missing). Estimation was done using the SAS procedure PROC PHREG.

Results

Overall, 5,752 women aged 45 years or less with primary breast cancer were identified. Since the specific aim of the study was to evaluate the prognostic effect of having a pregnancy subsequent to breast cancer treatment, we excluded 27 women who might have been pregnant at the time of diagnosis, i. e. women who

had a childbirth less than 10 months after the breast cancer diagnosis, or women who had an abortion with a gestational age indicating that they might have been pregnant at the time of diagnosis of breast cancer. This left 5,725 patients with a total of 35,067 person-years of follow-up for further study. Among these, 173 women (3.0%) experienced a total of 211 pregnancies (97 full-term pregnancies, 22 spontaneous abortions, and 92 induced abortions). Thirty-two women had more than one pregnancy after breast cancer diagnosis. The median time between breast cancer diagnosis and time of birth or abortion was as follows: a) birth 32 months (range 11-147 months), b) spontaneous abortion 23 months (range 6-50 months), and c) induced abortion 22 months (range 3-89 months). Distribution of patients according to histopathological tumour criteria, protocol allocation, and reproductive status after diagnosis of breast cancer is shown in Table 1. These factors plus the year of treatment and time since last previous childbirth, known to be of prognostic influence, were introduced in a multivariate analysis. The adjusted relative risk of dying according to reproductive history after treatment of breast cancer, age at diagnosis, and tumour characteristics is given in Table 2. Women with a full-term pregnancy after treatment of breast cancer had an insignificantly reduced risk of dying (RR: 0.55; 95% CI: 0.28-1.06, p=0.08) compared to other women with breast cancer. Women having induced abortion or spontaneous abortion experienced no significant risk alteration. Information on recurrence was available in the group of protocol-allocated patients (n=4,695 (82%)). If for this subgroup recurrence was introduced in the multivariate model, the relative risk estimate for women with full-term pregnancy was unchanged (RR: 0.79; 95% CI: 0.39-1.61).

Further analysis showed that the effect of subsequent pregnancy was not significantly modified by age at diagnosis, tumour size, nodal status, status as parous/nulliparous before diagnosis, time since most recent previous pregnancy before breast cancer diagnosis, age at subsequent pregnancy, or time to subsequent pregnancy (data not shown).

We subsequently performed a restricted analysis including only women who were classified as having a low-risk tumour (n=2,110). Also in this group of breast cancer patients, the survival was favourable for women with a full-term pregnancy subsequent to breast cancer treatment (RR: 0.61; 95% CI: 0.19-1.91) compared to other women with low-risk breast cancer. Calculated on the basis of the age-standardized incidence rates of childbirths in Danish women, the expected number of full-term pregnancies in the entire cohort was 285 compared with the observed 97.

Table 1. Distribution of 5,725 breast cancer patients, diagnosed 1978-95, according to age at diagnosis, tumour characteristics, protocol allocation, and reproductive status subsequent to their diagnosis. Danish women born after April 1, 1935 and less than 45 years of age at diagnosis.

	Reproductive status after diagnosis of breast cancer n (%)			
	Full-term pregnancy*	Induced abortion†	Spontaneous abortion	No pregnancy
Total No	84	77	12	5,552
Age at diagnosis				
<35 years	62 (74%)	35 (45%)	6 (50%)	603 (11%)
35-39 years	17 (20%)	29 (38%)	3 (25%)	1,436 (26%)
40-45 years	5 (6%)	13 (17%)	3 (25%)	3,513 (63%)
Tumour size				
2 cm	47 (56%)	42 (55%)	6 (50%)	2,876 (52%)
>2, 5 cm	17 (20%)	23 (30%)	4 (33%)	1,823 (33%)
> 5 cm	5 (6%)	4 (5%)	0 (0%)	414 (7%)
No information	15 (18%)	8 (10%)	2 (17%)	439 (8%)
Positive nodes				
0	49 (58%)	46 (60%)	7 (58%)	2,812 (51%)
1-3	19 (23%)	20 (26%)	4 (33%)	1,563 (28%)
4-9	6 (7%)	5 (6%)	0 (0%)	640 (12%)
10	0 (0%)	2 (3%)	0 (0%)	202 (4%)
No information	10 (12%)	4 (5%)	1 (8%)	335 (6%)
Histologic grading				
I	15 (18%)	16 (21%)	4 (33%)	1,270 (23%)
II + III	35 (42%)	45 (58%)	7 (58%)	3,058 (55%)
ND‡	34 (40%)	16 (21%)	1 (8%)	1,224 (22%)
Protocol allocation				
Yes	55 (65%)	65 (84%)	9 (75%)	4,556 (82%)
No				
Not treated according to surgical guidelines	21 (25%)	11 (14%)	3 (25%)	726 (13%)
Not allocated due to other reasons§	8 (10%)	1 (1%)	0 (0%)	270 (5%)

* Including 8 women with both induced abortion and full-term pregnancy, 5 women with spontaneous abortion and full-term pregnancy, and 1 woman with both induced abortion, spontaneous abortion and full-term pregnancy. †Including 1 woman with both induced abortion and spontaneous abortion. ‡Including patients with non-ductal carcinomas and patients without information on histologic grading. §Medical contraindications, bilateral breast cancer, distant metastasis, or inflammatory cancer.

Table 2. Adjusted relative risk (aRR) of dying according to reproductive status after diagnosis of breast cancer, age at diagnosis, and prognostic factors among 5,725 women.

Variables		aRR (95% CI)*
Reproductive status after diagnosis of breast cancer		
Full-term pregnancy	No	1 ref.
	Yes	0.55 (0.28-1.06)
Induced abortion	No	1 ref.
	Yes	1.00 (0.67-1.50)
Spontaneous abortion	No	1 ref.
	Yes	0.36 (0.09-1.45)
Age at diagnosis		
<35 years		1 ref.
35-39 years		1.01 (0.88-1.17)
40-45 years		0.93 (0.82-1.06)
Tumour size		
2 cm		1 ref.
>2. 5 cm		1.74 (1.54-1.96)†
> 5 cm		2.46 (2.06-2.93)†
Positive nodes		
0		1 ref.
1-3		1.60 (1.41-1.82)†
4-9		3.02 (2.60-3.50)†
10		4.06 (3.26-5.06)†
Histologic grading		
I		1 ref.
II + III		2.25 (1.92-2.64)†
ND‡		1.13 (0.93-1.37)

*Adjusted relative risk (95% confidence intervals) adjusted for the other characteristics listed above, year of treatment, protocol allocation, and time since last previous childbirth.
†$p<0.05$
‡Patients with non-ductal carcinomas.

Discussion

The present study documented that a pregnancy subsequent to treatment of breast cancer conferred no negative effect on the prognosis. Because women with a poor prognosis are believed to avoid pregnancies, there is a potential problem of the exposed group being selected. This problem is not easy to overcome and has been the main concern regarding the interpretation of results from previous studies on this subject [7-16]. The present investigation took advantage of the clinical population-based DBCG database that over many years has recorded detailed information on breast tumour characteristics. Also, in the present study the group of women with subsequent pregnancy tended to have smaller tumours and a slightly lower risk of nodal involvement. However, we were able to perform a detailed adjustment for the influence of such important prognostic factors and thus to mini-

mize selection bias. Furthermore, the use of time-dependent variables in a cohort design enabled us to adequately adjust for the important influence of time from breast cancer diagnosis to time of birth or abortion. Thus, the length of the relapse free period is believed to significantly influence the woman's decision regarding pregnancy. Women with known recurrence are not believed to get pregnant deliberately which might introduce a selection bias. However, the estimated relative risk of dying was not significantly influenced by the introduction of recurrence in the multivariate model.

The proportion of protocol-allocated patients was lower in the group of women who subsequently gave birth compared to other groups. This may partly be explained by some of these women choosing breast conserving therapy at a time when this treatment was not established as equal to mastectomy (before 1989). In those circumstances they have not been included in treatment protocols because they fell outside the surgical guidelines. However, we adjusted for this discrepancy by introducing protocol allocation in the multivariate analysis.

We acknowledge that despite these efforts, there are likely to be other selection mechanisms for which we were unable to adequately adjust with the available prognostic factors. This may explain why women with a full-term pregnancy subsequent to breast cancer treatment, even after adjustment for established prognostic factors, tended to have a better outcome than women without a subsequent pregnancy. Although we may not have completely adjusted for all factors, it seems implausible that we should have overlooked a negative prognostic effect of a pregnancy after breast cancer treatment. Thus, in a restricted analysis which included only women allocated to the low-risk group of breast cancer patients, we found women with a subsequent pregnancy to also have a favourable prognosis. The group of women allocated to the low-risk protocol constitutes a homogeneous population with localized disease unlikely to give symptoms that might influence a woman's decision regarding pregnancy. The risk of selection bias should therefore be particularly small in this group.

Certain reproductive factors such as age at first birth and time since last childbirth have been shown to have prognostic effect [5,6,22-24]. We were able to adjust for these factors in the analysis and furthermore to show that none of the reproductive factors modified the prognostic influence of pregnancy subsequent to treatment of breast cancer. The fertility rate, calculated on the basis of full-term pregnancies, was reduced to one third of the expected level in the group of treated breast cancer patients. This is due to an overall lower number of pregnancies as well as an increased incidence of induced abortions in this group of women. In Denmark, the number of induced abortions based on figures from the mid of our study period constituted 36% of the number of full-term pregnancies [25]. In our material breast cancer patients chose induced abortion almost as often as fulfilling pregnancy, whereas the number of spontaneous abortions was as expected. Unplanned pregnancy when a woman is seriously ill most likely leads to a higher rate of induced abortions. It is obvious that many women have avoided getting pregnant after their breast cancer diagnosis. Furthermore, it is possible that some women have chosen induced abortion due to lack of knowledge of the influence a pregnancy might ha-

ve on the course of their treated breast cancer. However, women with a history of induced abortion after breast cancer treatment did not have a different profile of prognostic factors than other women, which suggests that induced abortion was not chosen primarily among patients with a poor prognosis. This finding further supports the credibility of the overall result.

CONCLUSIONS

Based on the studies undertaken sofar the following conclusions were reached regarding topics covered under category I and III in the original application:

I. Abortion and breast cancer risk

Study 1: There is no overall effect of induced abortions on breast cancer risk. Our finding of a significantly increased risk in the special group of second trimester abortions was based on a limited number of cancer events and should be considered with caution. (Published in: *N Engl J Med 1997*; 336:81-85)

III. Factors influencing the prognosis of breast cancer

Study 2: A diagnosis of breast cancer less than two years after having given birth is associated with a particularly poor survival irrespective of the stage of disease at debut. Therefore, a recent pregnancy should be regarded as a negative prognostic factor, and as such be considered in the counselling of these patients and in the decisions regarding adjuvant treatment regimens. (Published in: *BMJ* 1997; 315: 851-55).

Study 3: Low age at first childbirth, but not parity, was associated with a poor prognosis of breast cancer. We speculate whether women who develop breast cancer despite an early first full-term pregnancy might represent a selected group with a particular malignant disease. (In press at: *Br J Cancer* 1998)

Study 4: We found no evidence that a pregnancy subsequent to breast cancer treatment should aggravate the prognosis. (Published in: *Lancet* 1997; 350:319-22).

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